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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/021,660	02/10/1998	MARGARET H. BARON	1874/110	4751

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	34

DATE MAILED: 11/15/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/021,660	Applicant(s) BARON ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-75 and 82-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-75 and 82-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/27/01 has been entered.

Renumbered Claims

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 80-111 have been renumbered 82-113.

Response to Arguments

The rejection under 35 USC 112, first paragraph, for written description is withdrawn in view of the amendments to the claims.

The rejection under 35 USC 112, second paragraph, is withdrawn in view of cancellation or amendment of the rejected claims.

The rejection under 35 USC 102(b) is withdrawn in view of the amendment to the claims.

Claim Interpretation

To reiterate from the Advisory Action of paper #28: Indian hedgehog, Desert hedgehog or Sonic hedgehog (Ihh, Dhh or Shh, see for example claim 82), are being interpreted by the Examiner to be limited to the meaning that these 3 types of "proteins consist of the amino acid sequence found in nature. That does not preclude these proteins from being recombinantly produced, but their amino acid sequence is the same as that found in the corresponding proteins isolated from an animal. This appears to agree with the use of the terms in the specification, where all references to, for example, Ihh, are to the protein with a sequence which is found in

nature *(e.g.* p. 20, lines 21-17). The meaning of these terms appears to be distinct from that of a "hedgehog compound" as defined on page 11, lines 23-26, which includes analogs and derivatives of hedgehog proteins."

Incorporation by Reference

Applicants have attempted to incorporate by reference. The matter added by amendment from the foreign patent is essential.

The attempt to incorporate essential subject matter into this application by reference to WO 95/18856 is improper because what is to be incorporated was broadly described in the instant specification as "hedgehog compounds... including homologs of hedgehog proteins, ...hedgehog encoding nucleic acids, antisense molecules,.. combinantorial mutants of hedgehog proteins as agonists or antagonist, and antibodies specific for hedgehog protein epitope." However, specific information in the form of SEQ ID NOs now relied upon in the claims (*e.g.* claim 57) is being added from WO 95/18856 to the specification, as well as newly added properties and characteristics relating to the sequences, for example, % homology. In the instant specification as filed, there was no direction to a specific portions of the WIPO patent.

"Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). The MPEP 608.01(p) states:

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

Specification

The amendment filed 8/27/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the

original disclosure is as follows: The sequences and description of sequence properties added from WO 95/18856 represent new matter because they were added by improper incorporation by reference (see above). The description of % identity or homology to sequences and hybridization as newly set forth is also new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

Claim 74 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Both claim 74 and claim 72 from which it depends have the claim limitation of the same modes of administration.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-75 and 82-113 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The sequences that the claims require were brought into the application by an improper incorporation by reference (see above). The original specification discloses only hedgehog proteins obtainable from natural sources.

Claim Rejections - 35 USC § 112

Claims 57-75 and 82-113 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating a population of undifferentiated mammalian mesodermally derived cells to undergo hematopoeisis or of stimulating

hematopoeisis in an animal, comprising contacting said cells or administering to the animal, respectively, an effective amount of Ihh, Dhh or Shh protein or a fragment thereof which binds to patched and induces cells to undergo hematopoiesis such that the protein or fragment thereof contacts undifferentiated mammalian mesodermally derived cells or hematopoietic stem cells, does not reasonably provide enablement for administration wherein the protein or fragment thereof does not specifically contact the above cell types and wherein the protein or fragment is not Ihh, Dhh, Shh or a fragment thereof which binds to patched and induces cells to undergo hematopoiesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are two scope of enablement issues with the present claims. 1)The claims as written have great breadth in terms of the compound applied to stimulation of hematopoiesis . 2) There is additionally breadth for claim 83 and dependent claims in that the type of cell contacted by the compound is undefined. The second issue will be addressed first.

The breadth of the claims added by the types of cells that may be undifferentiated mesodermally-derived cells is *not* great since the developmental lineage of such cells has been well known in the art and the specification provides guidance and examples of the types of cells that can be successfully used in the claimed method. The method of claim 83 does not require contact of mesodermally-derived cells, and neither the prior art nor the specification provides examples or guidance of how to promote hematopoeisis if such derived cells are not contacted. It would require undue experimentation to practice the claimed invention as it is not broadly written.

As to the first issue, it is noted that in the specification, a "hedgehog compound" (claim 57) is defined as a hedgehog protein or analog or derivative thereof or agonists or antagonists of

hedgehog protein receptors of functional equivalents of any of these. Therefore, such a compound need not have any resemblance to a naturally occurring Ihh, Dhh or Shh polypeptide except as it is not required to be at least 80% identical to or hybridize under certain conditions to one of the listed amino acid sequences for a naturally-occurring hedgehog protein. Between mammalian Shh proteins there is about 85% cross-species identity. Within the N-terminal half, there is about 99% identity. The instant claims encompass identity much lower than that even found in nature. Also, at the time the instant invention was filed, there was little known about which parts of a hh protein were responsible for activity. It was known that in many instances the N-terminal half of Shh was sufficient to cause the effects seen when the complete Shh was administered.

There are no examples of any compounds other than Shh, Ihh or BMP-4 stimulating the cells to undergo hematopoiesis. However, results from studies listed in the specification (page 20-21) using Ihh and Dhh knockout transgenic mice would lead the skilled artisan to reasonably expect that Dhh could also be used in the claimed method. The invention is drawn to a method of stimulating a population of undifferentiated mesodermally-derived cells (*e.g.*, hematopoietic stem cells, yolk sac mesoderm, with the exception of claim 83 and its dependent claims) to undergo hematopoiesis. While there are suggestions in the art of compounds which might induce hematopoiesis, the predictability about whether or not those compounds actually can is low. For example, it has been shown that mice embryos deficient in the flk-1 receptor (*i.e.*, a receptor for VEGF) have severely reduced hematopoiesis and vasculogenesis (Shalaby et al., EI, Nature, 1995). Nevertheless, it has not been shown that VEGF itself can induce hematopoiesis, although it has clearly been shown to induce vasculogenesis. The claims have great breadth because of the broad manner of reciting the hedgehog compound in the claims. For these reasons, it would require undue experimentation to practice the claimed invention.

For claim 75 and dependent claims, the first compound must be capable of acting synergistically with a second compound. The specification on page 11, line 20, defines a "Synergist effect" as "for two or more compounds where little or no biological effect is observed with the compounds alone but together the compounds have a potent biological effect." There is no teaching in the specification or the prior art of such compounds capable of having one of the required effects together where each compound alone as little or not effect.

Applicants' arguments that pertain to the new rejection above are addressed here.

Applicants argue that the Examiner has failed to show why one skilled in the art could not practice the claimed method with a hh polypeptide or any compound that is functionally equivalent to a hedgehog polypeptide. The argument has been fully considered, but is not persuasive. The issue is not of using functionally equivalent compounds, it is making and finding compounds that are functionally equivalent to Ihh, for example. Applicant has not provided or provided sufficient guidance to make a commensurate number of functionally equivalent compounds. The compound must have more than the function of binding *patched*. It must activate *patched*. Still further, that activation must lead to the necessary signal transduction cascade to cause stimulation of hematopoeisis. The method requires activation of a complex and probably multi-component pathway (for example activation of a BMP, see attached Bhardwaj et al., Nature Immunol., 2(2):172, Feb. 2001). As in the rejection above, it would require undue experiment to practice the method commensurate in scope with the claims as they encompass a great breadth of compounds.

Applicants argue that former claim 75 (amended claim 73) has been amended to conform to the teaches of the specification as to effect of administering TGF. The argument has been fully considered, but is not persuasive. Former claim 75 (and 74) are still pending. Only former claims 76-81 were cancelled.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 73, 82, 83, 85, 88, 95, 96, 99 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73, 82, 85 and 99 are indefinite because the metes and bounds of the claim cannot be determined due to the use of the term "TGF-β compound". The specification does not

provide a limiting definition for such compounds (p. 18, lines 23-27), and it is not clear what types of compounds are and are not included in that term.

Claim 57, 83, 88, 95 and 96 are indefinite because it is not clear what amount of the compound is being used. That is, there is a gap in the method if the amount of compound is not effective to produce the result required by the preamble. This rejection could be obviated by add "effective amount of" before "a hedgehog compound", for example.

Prior Art

The art made of record and not relied upon is considered pertinent to applicant's disclosure. Detmer et al. (Blood Cells, Molecules, and Diseases, 2000) supports the role of hedgehog in hematopoiesis, but also points to the amount of unknown information in the complex pathway by which hh causes erythroid cell differentiation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

November 13, 2001